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Stimulants and the developing brain

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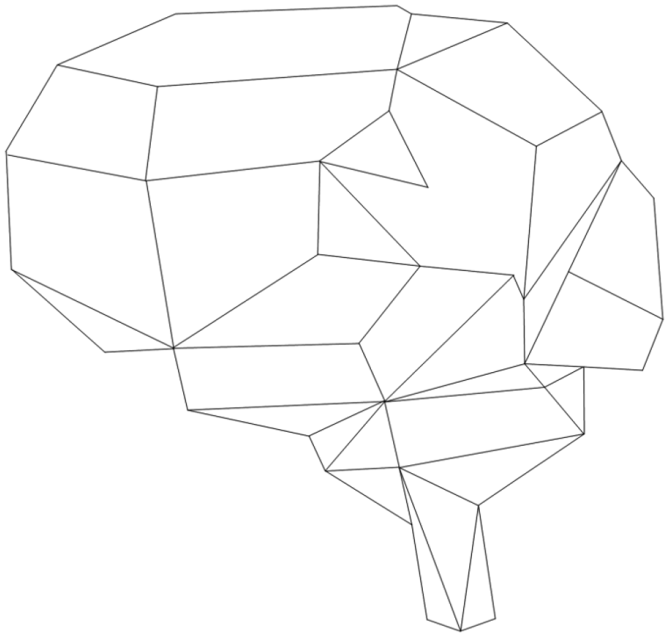
Chapter 3

THINNER MEDIAL TEMPORAL CORTEX IN CHILDREN WITH ADHD AND THE EFFECTS OF STIMULANTS



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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) has been associated with widespread changes in cortical thickness (CT). Findings have been inconsistent, however, possibly due to age differences between samples. Cortical changes have also been suggested to be reduced or disappear with stimulant treatment. We investigated differences in CT between adolescents/young adults with and without ADHD, in the largest ADHD sample to date, the NeuroIMAGE sample. Second, we investigated how such differences were related to age and stimulant treatment.

Methods: Participants (ADHD=306; healthy controls=184, 61% male, 8-28 years old, mean age=17) underwent structural magnetic resonance imaging. Participants and pharmacies provided detailed information regarding lifetime stimulant treatment, including cumulative intake and age of treatment initiation and cessation. Vertex-wise statistics were performed in Freesurfer, modeling the main effect of diagnosis on CT and its interaction with age. Effects of stimulant treatment parameters on CT were modeled within the ADHD sample.

Results: After correction for multiple comparisons, participants with ADHD showed decreased medial temporal CT in both left ($p_{CLUSTER}$=0.008) and right ($p_{CLUSTER}$=0.038) hemispheres. These differences were present across different ages, and were associated with symptoms of hyperactivity and prosocial behavior. There were no age-by-diagnosis interaction effects. None of the treatment parameters predicted CT within ADHD.

Conclusions: Individuals with ADHD showed thinner bilateral medial temporal cortex throughout adolescence and young adulthood compared to healthy controls. We found no association between CT and stimulant treatment. The cross-sectional design of the current study warrants cautious interpretation of the findings.

INTRODUCTION

Magnetic resonance imaging (MRI) has revealed structural and functional brain changes associated with attention-deficit/hyperactivity disorder (ADHD) (Bush et al., 2005; Frodl & Skokauskas, 2012; Nakao et al., 2011). Surface-based reconstruction of the cortical sheet allows quantification of different features of cortical structure, including volume, thickness, surface area, and curvature. Such features may represent distinct developmental processes having separate developmental trajectories (Raznahan et al., 2011). Changes in different features may be associated with distinct forms of psychopathology (Shaw et al., 2012). Volumetric studies have consistently reported global cortical volume reduction in individuals with ADHD (Greven et al., 2015; Nakao et al., 2011). Widespread reductions of cortical thickness (CT) have also been implicated in ADHD. Children and adults with ADHD have shown decreased CT in frontal cortex (Almeida et al., 2010; Hoekzema et al., 2012; Proal et al., 2011; Shaw et al., 2013; Yang et al., 2015), inferior and superior parietal cortex (Hoekzema et al., 2012; Narr et al., 2009; Proal et al., 2011), temporal pole and medial temporal cortex (Langevin et al., 2014; Proal et al., 2011). However, patterns of ADHD-related cortical changes differ widely across studies. There have been multiple reports of increased rather than decreased CT in individuals with ADHD (Almeida Montes et al., 2012; Duerden et al., 2012), and other studies have found no association between CT and clinical features of ADHD (Narr et al., 2009; Yang et al., 2015).

Discrepant patterns of CT changes in ADHD between studies may result from age differences in groups under study. ADHD often persists into adulthood (Copeland et al., 2013), typically showing reduced hyperactivity but persistent inattention throughout adolescence. In typical development, CT increases during childhood to reach its peak in early adolescence, after which it decreases again. The “maturational delay” hypothesis of ADHD proposes that CT changes observed in children with ADHD reflect the ADHD group lagging behind the typically developing group and reaching peak CT at a later age (Shaw et al., 2007a). As they grow older, adolescents with ADHD are proposed to “catch up” with their unaffected peers, resulting in fewer or no cortical changes along with a decline in clinical symptoms at later age (remission). The hypothesis is supported by an impressive longitudinal sample of children and adolescents, with an average age of twelve (Shaw et al., 2007a). A substantial proportion of children with ADHD, however, continues to have symptoms in late adolescence and adulthood (Faraone et al., 2006). Differences in CT in adults with ADHD have also been reported (Almeida Montes et al., 2012; Duerden et al., 2012), suggesting that cases of persistent ADHD do not show cortical normalization during late adolescence. Unfortunately, the majority of studies focused on either children or

adults, and the development of CT in (late) adolescent ADHD has not extensively been documented. One cross-sectional study found both increases and decreases in CT in older adolescents/young adults with ADHD (Almeida Montes et al., 2012). Zooming in on the late adolescent phase could aid in further elaboration of cortical development in ADHD.

A substantial proportion of individuals with ADHD are prescribed stimulants. MRI studies investigating the effect of methylphenidate treatment on brain volume and function in children with ADHD have suggested at least partially normalizing effects (Frodl & Skokauskas ,2012; Nakao et al., 2011; Rubia et al., 2014; Spencer et al., 2013). Very few have studied the effect of stimulants on CT. In a longitudinal study, Shaw et al. (2009) showed normalized developmental trajectories of CT in stimulant-treated, but not in non-treated children with ADHD. Treatment effects were local rather than global, affecting CT in the left dorsolateral prefrontal cortex, and right motor and posterior parietal cortex. By contrast, other studies have reported greater CT abnormalities in previously medicated patients (Narr et al., 2009), or observed no differences between stimulant-naïve and stimulant-treated patients (Hoekzema et al., 2012).

The investigation of long-term treatment effects in pediatric groups is complex. Long-term effects (spanning multiple years) may only be assessed in observational studies, in which ADHD cases have not been randomized over stimulant and non-stimulant treatment. This creates the possibility of confound by indication, i.e. non-stimulant treated cases may be less severe, or may differ from stimulant-treated cases in other ways. An advantage of observational studies, however, is that study samples are typically representative of the study population. To investigate stimulant treatment effects on brain structure, “treated” and “untreated” individuals with ADHD are typically compared. However, this distinction is rather crude, and neglects between-subject variation in treatment history. Whereas some classify past users as “treated” (e.g., Shaw et al., 2009), others may classify them as “untreated” (e.g., Amico et al., 2011) or exclude such participants (e.g., Onnink et al., 2014). Investigating treatment heterogeneity in more detail may reveal mechanisms by which stimulant treatment may affect brain structure.

In the current study we compared CT in a large sample of adolescents/young adults with ADHD (n=306) to that of a healthy control sample (n=184). Further, the linear and nonlinear effects of age on changes in CT associated with ADHD (if any) were investigated. Last, we tested the effect of multiple well-defined stimulant treatment parameters. The current study adds to the previous volumetric findings of our group of ADHD being associated with global rather than local volume reductions (Greven et al., 2015). Other neuroimaging studies based on the same sample investigated volumetric features (O’Dwyer et al., 2014; Schweren et al., 2015b, van

der Meer et al., 2015), structural connectivity (Francx et al., 2015; van Ewijk et al., 2014b and 2015), or functional MRI (Pruim et al., 2015a and 2015b; van Rooij et al., 2015a and 2015b). To the best of our knowledge CT has not previously been studied in an ADHD sample of this size.

METHODS

Participants

Participants were selected from the Dutch follow-up phase of the International Multicenter ADHD Genetics study (IMAGE; Mueller et al., 2011; Rommelse et al., 2008). ADHD diagnosis, ADHD severity, and presence of comorbid disorders were established using an algorithm based on both the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al., 1997) and Conners' ADHD questionnaires for parents, teachers, and adult participants (Conners et al., 1998a, 1998b, and 1999). See Von Rhein et al. (2015) and Supplement S1, for more details and relevant publications regarding the sample and diagnostic algorithm. IQ was estimated from the subtests "vocabulary" and "block design" of the Wechsler Intelligence Scale for Children – Version III (participants ≤ 16 years old) or the Wechsler Adult Intelligence Scale – Version III (participants > 16 years old; Wechsler, 2000 and 2002). The subtest "digit span" was administered as an indication of working memory capacity. In addition, the strengths and difficulties questionnaire for children was administered (SDQ; Van Widenfelt et al., 2003). Socio-economic status (SES) was calculated as the average (of both parents) number of years of education. Participants withheld use of psychoactive drugs for 48 hours prior to their visit. Informed consent was signed by all participants and parents (parents signed informed consent for participants < 12 years old). Testing took place at the University Medical Center of either Amsterdam or Nijmegen. The study was approved by the local ethical committee. The final sample consisted of 306 participants with ADHD and 184 healthy control subjects, between the ages of 8.3 and 27.8 years old ($M=17.05$, $SD=3.33$).

Assessment of medication history

Lifetime medication transcripts from pharmacies were available for 74%, and covered lifespan for 25% of participants with ADHD. In addition, a questionnaire was administered to all participants and parents assessing lifetime history of psychoactive medication. When pharmacy transcripts did not fully cover the self-reported treatment period, medication parameters of the missing period(s) were calculated

from the questionnaire data, and were added to the measures derived from the pharmacy. Retrospective assessment of ADHD medication has shown good to excellent concordance between parent- and physician-report even after multiple years (Kuriyan et al., 2014). The following indices of stimulant treatment (methylphenidate immediate/extended release, and d-amphetamine preparations) were calculated: history of treatment (stimulant-exposed vs. stimulant-naïve); start age; stop age; median age of exposure (age in years at the median of all exposed days); treatment duration corrected for age (treatment duration divided by [age minus the minimum start-age within the sample, i.e. age 2.3]); mean daily dose (average dose in mg for all exposed days; d-amphetamine dose was multiplied by two); cumulative intake corrected for age (corrected treatment duration multiplied by mean daily dose); and time since last treatment (age minus stop age). For stimulant-naïve patients, mean daily dose, treatment duration and cumulative intake were zero; start age was imputed as the participant's age at scan (mimicking late initiation), and stop age was imputed as age 2.3 (mimicking early cessation).

MRI acquisition and analysis

MRI data was acquired at 1.5T on a Siemens Sonata scanner at the University Medical Center in Amsterdam, and on a Siemens Avanto scanner in Nijmegen, with an identical 8-channel phased array coil and identical acquisition parameters. There were no major hardware upgrades on either of the scanners during the study. Comparability of MRI data from the two sites has extensively been described elsewhere (Von Rhein et al., 2015). Scanning parameters and quality assurance procedures are described in Supplement S1. Cortical reconstruction was performed with Freesurfer (Dale et al., 1999; Fischl et al., 1999 and 2004). Freesurfer is an automated technique to create a 3D reconstruction of the cortical sheet that uses both intensity and continuity information, with good test-retest reliability across scanner stations (Han et al., 2006). CT was calculated for each vertex on the reconstructed cortical sheet, and defined as the closest distance from the gray/white boundary to the gray/CSF boundary (Fischl & Dale, 2000). Cortical surface area, used in post-hoc analyses, was measured at the geometric middle between the inner and outer cortical surfaces. A 10mm FWHM surface-based smoothing kernel was applied. Average CT per subject was calculated across all vertices. Total brain volume was calculated as the sum of Freesurfer estimated total grey and white matter volume.

Data analysis

Statistical modeling was performed with the glmfit-tool embedded in Freesurfer, and in second instance in SPSS version 20.0.0.0 (IBM, 2013). The effects of diagnostic group (healthy controls vs. participants with ADHD) and stimulant exposure (stimulant-exposed vs. stimulant-naïve) on CT were analyzed in a linear main effects model including gender, scanner location, and SES as covariates, and age and age^2 as optional per-vertex covariates. Optimal modeling of age as a covariate across the cortex was obtained in a two-step approach: First, between-group differences were evaluated with both age and age^2 in the model in all vertices where age^2 significantly contributed to the prediction of CT. Second, in all other vertices, age was kept in the model only where it significantly contributed to the prediction of CT. As a result, each vertex contained either a quadratic, a linear, or no effect of age (Figure S2). IQ was not added as a covariate in the primary analyses, since we consider lower IQ to be part of the ADHD phenotype (Dennis et al., 2009). In two additional vertex-wise models, we tested age-by-diagnosis and age^2-by-diagnosis interactions.

Comparing stimulant-exposed to stimulant-naïve participants allowed detection of between-group differences of medium effect size ($N_{EXPOSED}$=270, $N_{NAÏVE}$=36; two-tailed alpha=0.05, power=0.80, smallest detectable Cohen's d effect size=0.50). We further investigated treatment effects by vertex-wise linear modeling of continuous treatment variables within the ADHD sample, i.e. treatment duration corrected for age, mean daily dose, cumulative intake corrected for age, start age, stop age, median age of exposure, and time since last treatment. These parameters were initially tested in seven separate models, predicting CT with gender, scanner location, SES, age and age^2 as covariates (Bonferroni correction, cluster-wise alpha/7), and then simultaneously for those treatment parameters significantly predicting CT. Unlike in the case-control analyses, linear and quadratic age-terms were included for each vertex, as they were expected to be correlated with the predictor variables. With this approach regression coefficients of small to medium effect size could be detected (N_{TOTAL}=290; per vertex: two-tailed alpha=0.007, power=0.80, smallest detectable Cohen's f^2 effect size =0.067).

We applied Monte Carlo simulation testing (10.000 iterations, vertex-wise threshold $p<0.01$, cluster-wise threshold $p<0.05$) to correct for multiple comparisons. Within each significant cluster, mean CT and surface area were extracted for each participant in standard space, to perform post-hoc and sensitivity analyses in SPSS. We reported cluster size and p-value from the Monte Carlo simulation testing in Freesurfer, and estimated marginal mean CT per group and Cohen's d effect size from the SPSS analyses.

Exploratory post-hoc analyses were performed to investigate clinical correlates of case-control differences or treatment effects within participants with

ADHD (n=306). In separate linear mixed effects models, mean CT within each cluster was predicted by number of hyperactivity symptoms, number of inattention symptoms (both derived from the K-SADS interview and Conner's questionnaires), four subscales of the SDQ (conduct problems, emotional problems, peer problems, and prosocial behavior), working memory capacity (maximum digit span backwards), and IQ. Gender, scanner site, SES, and if appropriate age and age^2, were used as covariates. Second, we tested whether cortical surface area was affected in clusters of significant between-group or treatment effects. Last, for each significant cluster we tested age-by-diagnosis, age^2-by-diagnosis, and age-quintiles-by-diagnosis interactions effects.

Sensitivity analyses were performed to investigate the robustness of our findings. First, a random intercept per family was added to the model to account for dependencies among participants from the same family. Further sensitivity analyses entailed repeating each analysis with IQ, average CT, and total brain volume as additional covariates, respectively, and repeating each analysis within subgroups, i.e. within each of the two scanning sites, within boys and girls, within five age quintiles (age<14.05; age=14.06-16.21; age=16.22-18.01; age=18.02-20.04; and age>20.04), within participants who had never received psychoactive treatment other than stimulants, and within participants without any comorbid diagnoses (Table S3). Furthermore, vertex-wise analyses in Freesurfer were repeated with IQ, average CT, and total brain volume as covariates to allow detection of additional clusters (Table S4 and Figure S4).

TABLE 1. Demographic and clinical information of participants with and without ADHD.

	HC		ADHD		
	n	**%**	**n**	**%**	**p**
Participants	184	37.6	306	62.4	
Male	92	50.0	209	68.3	0.001
Amsterdam	116	63.0	135	44.1	0.001
	M	**SD**	**M**	**SD**	**p**
Age	16.77	3.15	17.23	3.43	0.138
IQ	106.16	13.75	97.05	15.24	0.001
SES	13.33	2.50	11.61	2.23	0.001

HC, healthy controls; SES, socio-economic status.

RESULTS

Demographic and clinical information

Compared to healthy controls, participants with ADHD were more likely to be male, to have participated in Nijmegen, and had lower SES and IQ (Table 1). Forty-four percent of participants with ADHD were of combined type (n=134). Thirty-three percent of participants with ADHD had a comorbid disorder (n=100), mostly oppositional defiant disorder and/or conduct disorder (n=91, 29.7%) but also tic disorders (n=3, 1.0%) and anxiety/depression (n=11, 3.6%). Eighty-eight percent (n=254) of participants with ADHD had received stimulant treatment at some point in their lives, including immediate-release (n=245, 84.5%) and/or extended-release (n=201, 69.3%) methylphenidate preparations and/or dexamphetamine (n=25, 8.6%). Compared to stimulant-naïve participants, stimulant-exposed participants were more likely to be male, to have participated in Nijmegen, were younger, and had lower IQ and more hyperactivity-impulsivity symptoms (Table 2).

Medication parameters could be calculated for the majority of participants with ADHD (N=290, 94.5%; including 254 stimulant-exposed participants, 87.6%). On average stimulant-exposed participants had received 4.9 years of stimulant treatment (SD=3.19; range 0.05-14.17) corresponding to 33% of their lives. They started stimulant treatment, on average, at age 8.5 (SD=2.75; range 2.30-20.61), and received a mean dose of 34 mg per day (SD=12.47; range 10.00-78.52). Forty-nine percent (n=125) of stimulant-exposed participants had ceased treatment at least three months and on average 1.6 years prior to study participation, with an average stop age of 15.5 years (SD=3.27; range 4.86-23.38). Twenty-eight percent (n=81) of all participants had received psychoactive medication other than stimulants, including atomoxetine (n=39, 13.5%), clonidine (n=18, 6.2%), antidepressants (n=16, 5.5%), atypical antipsychotics (n=48, 16.6%), and benzodiazepines/anxiolytics (n=15, 5.2%).

CT in participants with ADHD vs healthy controls

Participants with ADHD showed decreased CT in the medial temporal cortex in both left (cluster size=468mm^2; $p_{CLUSTER}$=0.008; Cohen's d effect size=0.443; CT_{HC}=3.323mm; CT_{ADHD}=3.182 mm) and right hemisphere (cluster size=368mm^2; $p_{CLUSTER}$=0.038; Cohen's d effect size=0.445; CT_{HC}=3.224mm; CT_{ADHD}=3.113mm; Figure 1). These case-control differences were significant after accounting for dependencies among participants from the same family, were present in both testing

TABLE 2. Characteristics of the exposed and unexposed participants with ADHD.

	Exposed		Unexposed		
	n	%	n	%	p
Participants	270	88.2	36	11.8	
Male	192	71.1	17	47.2	0.004
Amsterdam	104	38.5	31	86.1	0.001
Combined type	122	45.2	12	33.3	0.178
Comorbid disorder	89	33.0	11	30.6	0.772
ODD/CD	82	30.4	9	25.0	0.508
Tic disorder	3	1.1	0	0.0	0.525
Anxiety / Depression	9	3.3	2	5.6	0.501
	M	SD	M	SD	p
Age	17.04	3.23	18.61	4.45	0.048
IQ	96.42	14.84	101.75	17.43	0.049
Number of symptoms	13.36	2.93	11.55	3.13	0.001
Inattentive	7.34	1.71	6.75	1.59	0.053
Hyperactive-impulsive	6.03	2.30	4.89	2.80	0.024
SES	11.60	2.25	11.69	2.12	0.813

ODD/CD, oppositional defiant disorder/conduct disorder; SES, socio-economic status.

sites and both genders, remained significant when participants with comorbid diagnoses or psychoactive medication other than stimulants were excluded, and when IQ, total brain volume, and average CT (respectively) were added to the model as additional covariates (Table S3). In vertex-wise analyses with IQ and average CT as an additional covariate, a left superior parietal cluster of increased CT in participants with ADHD reached significance as well (Table S4 and Figure S4). In the primary analyses, the same pattern was observed but failed to reach significance after correction for multiple testing (data not shown).

Age^2 did not contribute to the prediction of CT in either of the medial temporal clusters, and the linear age term contributed in the right but not the left hemisphere cluster (Figure S2). CT of the ADHD and healthy control groups within each cluster was plotted in five age quintiles (Figure 2). The direction of effect remained unchanged in all age groups, and there were no age-by-diagnosis (p_{LEFT}=0.137, p_{RIGHT}=0.328) or age-quintile-by-diagnosis (p_{LEFT}=0.085, p_{RIGHT}=0.135) interaction effects. In accordance, we found no age/age^2-by-diagnosis interaction effects in vertex-wise analyses. There was no between-group difference in cortical surface area within the left (p=0.241) or right (p=0.166) cluster. Main effects of gender, site, and SES are in Table S2.

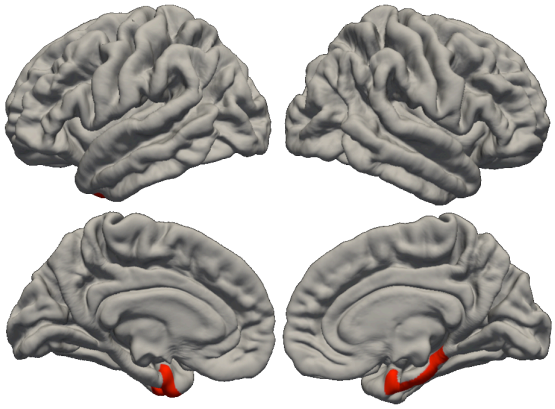

FIGURE 1. Regions of significant decrease in cortical thickness (cluster-wise p-value < 0.05, corrected for multiple comparisons using Monte Carlo simulation testing), in participants with ADHD compared to healthy controls, indicated in red and projected on the pial surface of a standard brain template (fsaverage). There were no regions of increased cortical thickness in participants with ADHD.

Stimulant exposure

There were no differences in CT between stimulant-treated and stimulant-naïve participants with ADHD. Treatment duration corrected for age, mean daily dose, cumulative intake corrected for age, start age, stop age, median age of exposure, and time since last treatment did not predict CT within the ADHD sample.

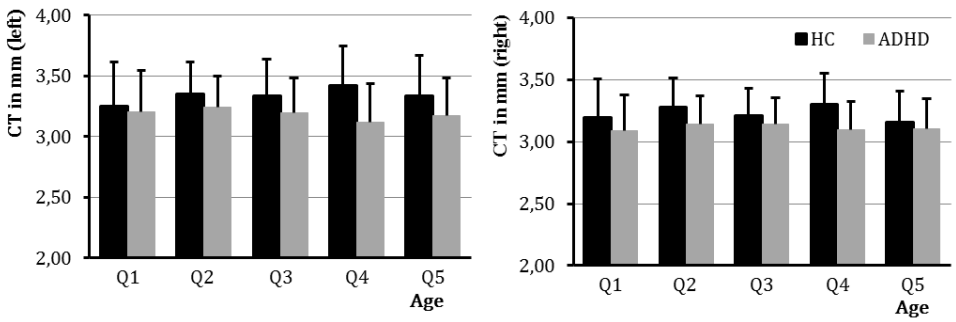

FIGURE 2. Cortical thickness (CT) in participants with attention-deficit/hyperactivity disorder (ADHD) and healthy controls (HC), stratified by age quintiles (Q1<14.05y; Q2=14.06-16.21y; Q3=16.22-18.01y; Q4=18.02-20.04y; Q5>20.04y) within the medial temporal clusters of case-control difference. Age-quintile-by-diagnosis interaction effects are not significant. Error bars represent standard deviations.

Post-hoc analyses: clinical correlates

Exploratory post-hoc analyses indicated that in participants with ADHD, CT within the left medial temporal cluster was related to number of hyperactivity symptoms (β=-0.039; p=0.020), but not to number of inattention symptoms (p=0.571), conduct problems (p=0.183), emotional problems (p=0.200), peer problems (p=0.562), prosocial behavior (p=0.647), working memory capacity (p=0.651), or IQ (p=0.730). Within the right medial temporal cluster, CT was related to prosocial behavior (β=0.031; p=0.034) but not to symptoms of inattention (p=0.985), hyperactivity (p=0.246), conduct problems (p=0.979), emotional problems (p=0.971), peer problems (p=0.768), working memory capacity (p=0.789) or IQ (p=0.817).

DISCUSSION

The current study investigated CT among adolescents and young adults with ADHD, and its associations with age and stimulant treatment. We found bilateral decreased medial temporal CT in participants with ADHD compared to healthy control participants. These differences were present across different ages, were not accompanied by changes in cortical surface area, were not driven by global brain changes, and were associated with symptoms of hyperactivity and prosocial behavior. Despite having the largest ADHD sample to date with substantial within-subject treatment variability, we found no association between CT and stimulant treatment history.

Reduced CT in medial temporal regions, including the hippocampus, amygdala, and parahippocampal cortex has previously been reported in pediatric

(Fernández-Jaén et al., 2014; Narr et al., 2009; Shaw et al., 2006) and adult (Proal et al., 2011) ADHD groups. Smaller medial temporal volumes have been associated with impaired response inhibition in individuals with ADHD (McAlonan et al., 2009), and structural changes of the hippocampus and amygdala have been associated with emotional dysregulation (Frodl et al., 2010; Posner et al., 2014). In a volumetric study of the current sample, a decrease in overall grey matter volume but no changes in hippocampal or amygdalar volumes were detected in participants with ADHD (Greven et al., 2015). Discrepant findings may be expected, however, since cortical volume is determined by cortical thickness as well as other parameters (i.e., surface area and gyrification). In addition, analyses of regional cortical volumes (including the hippocampus) in the volumetric study were corrected for global brain changes. Smaller hippocampal volumes may have been masked by the reduction in total brain volume in participants with ADHD (Greven et al., 2015). In the current study, adding global brain measures did not change our findings, suggesting that decreased medial temporal CT may not be related to global changes. Our findings add to the growing body of evidence suggesting that regions outside the frontal-striatal circuits may be important in the pathophysiology of ADHD (Kobel et al., 2010). Our exploratory and preliminary post-hoc analyses suggest a link between left medial temporal CT and hyperactivity symptoms, a core feature of ADHD. The clinical relevance of decreased medial temporal CT is to be further elaborated in future studies, in which hyperactivity and prosocial behavior but also typical medial temporal functions such as memory should be addressed.

The current study being cross-sectional, any findings regarding developmental changes or age effects should be interpreted with caution. Nevertheless, our study provides several interesting findings regarding age and ADHD. First, both clusters of case-control difference occurred (at least partially) in regions where CT was not related to age (Figure 2). In most other vertices, CT decreases with increasing age (Figure S2). Case-control differences thus occur in the absence of developmental changes in CT. Second, we found no age-by-diagnosis or age^2-by-diagnosis interaction effects. Thus, the medial temporal case-control differences are equally driven by younger and older participants. The developmental delay hypothesis proposes that, later in development, some children with ADHD "catch up" with their typically developing peers (Shaw et al., 2007a), resulting in smaller cortical abnormalities accompanied by (at least partial) clinical remission. This hypothesis could not be tested in the current study, since no cases of remittent ADHD were included. We emphasize again the cross-sectional nature of the current study. As a group, the older participants with ADHD may differ from the younger ones. A sizeable portion of participants within the younger ADHD groups may remit during adolescence, whereas this has not occurred in the older ADHD groups. This more

heterogeneous composition of the younger age groups may have masked any age-by-diagnosis interaction effects. There is a clear need for long-term longitudinal studies to characterize cortical development associated with persistence and remission of ADHD during late adolescence/young adulthood.

Despite having sufficient power to detect even small effects, we found no associations between stimulant treatment and CT. Any treatment parameter, regardless of its correlations with the other parameters, would have shown its individual effect (if any) in our initial approach of modeling each parameter separately. The absence of stimulant treatment effects has two implications for our findings. First, it aids the interpretation of the case-control differences. As the ADHD sample consisted largely of stimulant-exposed participants with an average treatment duration of almost five years, any case-control differences we observed may have been the result of stimulant treatment rather than associated with the ADHD phenotype. Two recent studies both reported hippocampal volume reduction in adults with ADHD who had during childhood been treated with stimulants, but not in stimulant-naïve adults with ADHD (Frodl et al., 2010; Onnink et al., 2014). The lack of association between stimulant treatment and CT within our ADHD group, however, renders this explanation less plausible.

Second, our findings do not support with the hypothesis of CT normalization with stimulant treatment. Most previous studies suggesting structural normalization with stimulant treatment reported cortical volume rather than thickness, of which two recent studies found evidence in meta-regression analyses (Frodl & Skokauskas, 2012; Nakao et al., 2011). In one study, development of CT over time was found to be normalized in participants with ADHD who received stimulant-treatment (n=24) compared to those who did not (n=19). These effects were confined to specific brain regions, including the left dorsolateral prefrontal cortex (Shaw et al., 2009). In a larger study of the same group, however, no stimulant treatment effects were found (Shaw et al., 2013). We found no evidence of stimulant treatment being associated with CT. Possibly, long-term stimulant treatment affects cortical volume but not thickness. Long-term treatment effects across different cortical features are an interesting opportunity for future studies.

The current study had several strengths. First, our sample comprised older adolescents and young adults, an age group that has received very little attention in previous studies. Second, as pediatric long-term treatment effects cannot be studied in randomized clinical trials, the current study took advantage of its observational nature. This resulted in a large and representative sample, allowing a detailed investigation of between-subject variation in treatment history. Third, access to pharmacy records allowed exact quantification of lifetime stimulant exposure. This extent of detail has rarely been accomplished in previous studies. Our study had

limitations too. The study was cross-sectional. An optimal design to investigate long-term outcomes would be longitudinal and include a pre-treatment measurement. In accordance, an optimal study design would include individuals with remitted ADHD as well. Second, few participants with ADHD were naïve to stimulants, and the average treatment duration of the ADHD sample was relatively long. Future studies of treatment effects would benefit from targeted inclusion of additional stimulant-naïve individuals. Third, the large sample size did not allow manual editing of the Freesurfer segmentations, which may have affected reconstruction of the cortical surface especially in the anterior temporal lobes. However, we expect such distortions, if any, to be small and randomly distributed across the participant groups.

In conclusion, we found reduced CT in bilateral medial temporal cortex in youths with ADHD compared to healthy controls. There were no age-by-diagnosis interaction effects. These findings suggest ADHD-related changes in CT existing throughout adolescence and young adulthood, and add to our prior report of overall grey matter volume reduction. In the largest ADHD sample to date, we found no evidence that CT was affected by stimulant treatment. Our cross-sectional findings suggest the importance of medial temporal regions in adolescent ADHD, and highlight the need for longitudinal studies of ADHD extending into late adolescence and young adulthood.

SUPPLEMENTAL INFORMATION

S1 – The IMAGE-NeuroIMAGE sample and MR parameters

Three-hundred-thirty-one ADHD families and 153 control families participated in a diagnostic interview, questionnaires, and extensive MRI scanning. The following inclusion criteria applied for all participants in the current study: participants had to be (1) between 8-30 years old at follow-up, (2) of European Caucasian descent, (3) have an IQ $\geq$ 70, (4) have no diagnosis of epilepsy, general learning difficulties, brain disorders and known genetic disorders (such as Down syndrome), (5) have no contraindication to MR scanning, and (6) show no incidental findings on the MRI scan. Healthy control participants had to fulfill the following additional criteria: no current or past mental health care utilization, no sibling(s) with any past or current psychiatric diagnosis, and no current or past psychoactive medication use. As recruitment was family-based, multiple members of one family could be included in the same diagnostic group. Unaffected siblings of participants with ADHD were excluded. Previous relevant publications from our group regarding the same sample that are not in the reference list included a study focusing on working memory (van Ewijk et al., 2014a) and another on the risk of developing substance use disorder in relation to stimulant treatment (Groenman et al., 2013).

Structural MRI acquisition consisted of two T1-weighted 3D MP-RAGE scans (TI = 1000 ms, TR = 2730 ms, TE = 2.95 ms, FA = 7°; Parallel imaging by generalized autocalibrating partially parallel acquisition (GRAPPA); 176 sagittal slices, voxel size 1 x 1 x 1 mm, FOV = 256 x 256 x 176 mm). For each participant, the structural acquisition of highest quality was selected by visual inspection (Blumenthal et al., 2002), accepting only scans with no/mild distortions. To assure Freesurfer reconstruction quality, the following reconstructions were subjected to visual inspection to detect regions of "flattened" or "spiky" surface and surface-holes: (1) twenty percent (randomly selected) of the sample; (2) all reconstructions based on a structural scan with mild distortions. Reconstructions that did not meet quality criteria were excluded from all analyses; no manual edits were made.

S2 - Covariates

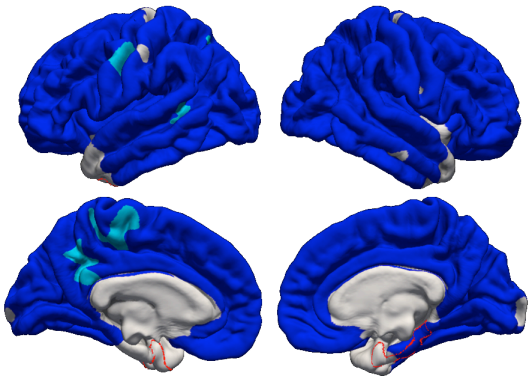

FIGURE S2.
Clusters of significant main effects of the linear and quadratic age terms (light- and dark-blue, respectively; corrected for multiple comparisons using Monte Carlo simulation testing). Increasing age was associated with decreasing cortical thickness. There were no regions of increasing cortical thickness with increasing age. The two medial temporal clusters of case-control difference are delineated in red.

TABLE S2. Gender, scanner and socio-economic status. Clusters of significant main effects of covariates gender, scanner site and socio-economic status (p_{vertex}=0.01, $p_{cluster}$=0.05, corrected for multiple testing), tested in the full model (cortical thickness is predicted by diagnostic status, scanner site, gender, socio-economic status, age and age^2).

Covariate	Direction	Hemi	Region	Size	T_{MAX}	$P_{CLUSTER}$
Gender	Boys > Girls	R	Lingual cortex	522.67	-4.578	0.00480
		L	Precentral cortex	374.89	-6.175	0.03100
		R	Insula	439.79	-5.401	0.01300
		R	Superior temporal cortex	475.71	-4.982	0.00820
		L	Middle frontal cortex	353.99	-4.629	0.04050
	Girls > Boys	R	Posterior cingulate cortex	499.60	6.114	0.00610
		L	Postcentral cortex	577.36	4.980	0.00230
		R	Precentral cortex	360.60	3.398	0.04190
		R	Inferior parietal cortex	410.96	5.105	0.01930
		R	Medial orbitofrontal	458.62	6.134	0.00960
SES	Neg	R	Lateral occipital cortex	434.31	-3.013	0.01340
Scanner site	AMS < NIJM	R	Middle temporal cortex	1196.71	-15.618	0.00010
		L	Middle temporal cortex	3396.30	-17.608	0.00010
		R	Middle frontal cortex	7402.56	-12.716	0.00010
		L	Middle frontal cortex	9300.90	-14.960	0.00010
	NIJM < AMS	R	Inferior parietal cortex	529.24	3.065	0.00400
		L	Superior parietal cortex	8971.47	7.844	0.00010
		R	Middle frontal cortex	896.99	4.627	0.00010
		L	Middle frontal cortex	2012.35	6.515	0.00010
		R	Precuneus cortex	3257.91	8.543	0.00010
		R	Supramarginal cortex	894.47	4.618	0.00010

R = right, L = left, Size = cluster size in mm^2, $P_{CLUSTER}$ = cluster-wise p-value after correction for multiple comparisons, AMS = scanner in Amsterdam, NIJM = scanner in Nijmegen, Pos = positive correlation, Neg = negative correlation, SES = socio-economic status.

TABLE S3. Sensitivity analyses. Estimated marginal mean cortical thickness in subsamples of healthy control participants and participants with ADHD, and associated p-values, within the left and right medial temporal cluster of significant case-control difference.

		LH			RH		
	n	EMM_{HC}	EMM_{ADHD}	p	EMM_{HC}	EMM_{ADHD}	p
Original analyses / all subjects	490	3.323	3.182	0.001	3.224	3.113	0.001
Within Amsterdam	251	3.347	3.221	0.003	3.207	3.136	0.028
Within Nijmegen	239	3.306	3.140	0.001	3.256	3.092	0.001
Within boys	301	3.342	3.191	0.001	3.222	3.110	0.001
Within girls	189	3.304	3.178	0.014	3.238	3.113	0.002
Within age < 14.05	99	3.252	3.201	0.526	3.198	3.092	0.120
Within age 14.05-16.21	98	3.347	3.242	0.060	3.278	3.144	0.007
Within age 16.21-18.01	98	3.335	3.197	0.037	3.211	3.142	0.162
Within age 18.01-20.04	97	3.416	3.119	0.001	3.304	3.094	0.001
Within age > 20.04	98	3.336	3.173	0.031	3.156	3.100	0.334
Excluding co-medication	401	3.326	3.184	0.001	3.221	3.117	0.001
Excluding co-morbidity	389	3.326	3.193	0.001	3.224	3.115	0.001
Additional covariate: IQ	490	3.321	3.184	0.001	3.227	3.112	0.001
Additional covariate: TBV	490	3.323	3.183	0.001	3.224	3.113	0.001
Additional covariate: average CT	490	3.318	3.185	0.001	3.223	3.116	0.001

RH = right hemisphere, LH = left hemisphere, EMM = estimated marginal mean cortical thickness in mm, HC = healthy control participants, ADHD = participants with attention-deficit/hyperactivity disorder, p = cluster-wise p-value after correction for multiple comparisons, TBV = total brain volume, CT = cortical thickness

S4 – Vertex-wise analyses with additional covariates.

TABLE S4. Participants with ADHD vs. healthy control participants. Regions of significant increased and decreased cortical thickness (cluster-wise p-value < 0.05, corrected for multiple comparisons using Monte Carlo simulation testing), in participants with ADHD compared to healthy control participants, in a statistical model including estimated IQ, total brain volume or average cortical thickness as an additional covariate.

Additional covariate	Region	Cluster size	$P_{CLUSTER}$	Cohen's d	EMM_{HC}	EMM_{ADHD}
IQ	L medial temporal	435.07	0.012	0.415	3.355	3.214
	R medial temporal	357.37	0.043	0.436	3.235	3.117
	L superior parietal	359.33	0.037	-0.434	2.091	2.204
Average CT	L medial temporal	440.36	0.006	0.417	3.334	3.199
	R medial temporal	340.71	0.032	0.449	3.229	3.117
	L superior parietal	385.43	0.014	-0.475	2.094	2.200
TBV	L medial temporal	475.00	0.009	0.425	3.349	3.207
	R medial temporal	390.75	0.028	0.419	3.184	3.073

CT = cortical thickness, TBV = total brain volume, R = right, L = left, $P_{CLUSTER}$ = cluster-wise p-value after correction for multiple comparisons, EMM = estimated marginal mean cortical thickness in mm, HC = healthy control participants, ADHD = participants with attention-deficit/hyperactivity disorder.

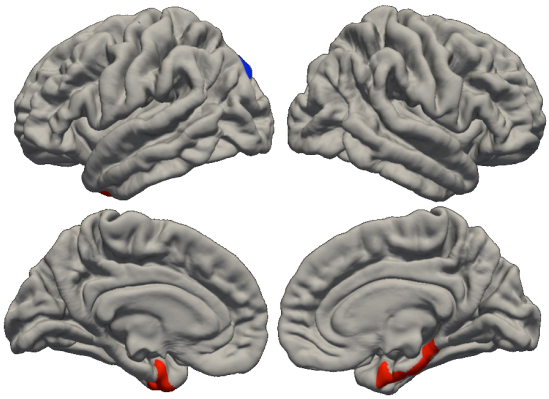

FIGURE S4.
Regions of significant decreased cortical thickness in red and increased cortical thickness in blue (cluster-wise p-value < 0.05, corrected for multiple comparisons using Monte Carlo simulation testing), in participants with ADHD compared to healthy control participants, in a statistical model including estimated IQ as an additional covariate.